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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/395,677	09/13/99	BERGER	D P-4579

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EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
1655	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/395,677	Applicant(s) BERGER ET AL.	
	Examiner BJ Forman	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 18-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

SUPPLEMENTAL DETAILED ACTION

Continued Prosecution Application

1. The request filed on 21 February 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/395,677 is acceptable and a CPA has been established. An action on the CPA follows.

2. The Amendments filed 28 December 2000 in Paper No. 10 in which claim 13 was amended and claims 1-12 & 17 were canceled is acknowledged. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 8 dated 22 September 2000 under 35 U.S.C. 112, first paragraph: New Matter are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) are withdrawn in view of the amendments. The arguments regarding the rejections under 35 U.S.C. 112, first paragraph: New Matter and under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) have been considered but are deemed moot in view of the withdrawn rejections. New grounds for rejection are discussed.

Applicant is reminded that changes to 37 C.F.R. § 1.121 require applicant to submit a clean set of all pending claims in addition to the marked up version of the amended claims.

Currently claims 13-16 & 18-32 are under prosecution.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

First paragraph of 35 U.S.C. 112: New Matter

4. Claims 13-16 & 18-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims as amended are drawn to a method for stabilizing the structure and nucleic acids of at least one cell in a sample comprising adding to a vessel containing the sample a composition comprising a first substance having a concentration effective for precipitating or denaturing protein, comprising at least one alcohol or ketone whose concentration is less than 80% of the total composition; and a second facilitator substance having a concentration effective for aiding in the infusion of the first substance into said at least one cell whose concentration is greater than 20% of the total composition. The claimed composition encompasses composition concentrations not disclosed in the specification i.e. a first substance of concentrations 0.001% to 79.99% and the second substance having concentrations of 20.001% to 99.99%. The specification teaches the preferred embodiment is 50% methanol/50% DMSO (page 4, lines 19-24). Additionally, the specification teaches 80% methanol/20% DMSO; 50% methanol/50% DMSO; and 100% methanol; 40% methanol + 40% ethanol/ 20% DMSO; 25% methanol + 25% ethanol/ 50% DMSO; and 80% ethanol/20%DMSO; 20% methanol/80% DMSO; 40% methanol/60% DMSO; 60% methanol/40% DMSO; 100% methanol; and 100%DMSO (Examples 4-12, pages 14-19, 21 & 23). However, the specification does not teach the broadly claimed compositions i.e. a first substance of concentrations 0.001% to 79.99% and the second substance having concentrations of 20.001% to 99.99% (e.g. 78% alcohol/ 22% DMSO). Therefore the claims, as amended, introduce new matter not disclosed in the specification as originally filed. It is suggested that the claims be amended to claim the invention as recited in the specification as originally filed.

First paragraph of 35 U.S.C. 112: Written Description

5. Claims 13-16 & 18-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims, as amended, are drawn to a method for stabilizing the structure and nucleic acids of at least one cell in a sample the method comprising: adding to a vessel containing the sample a composition comprising a first substance having a concentration effective for precipitating or denaturing protein, comprising at least one alcohol or ketone whose concentration is less than 80% of the total composition; and a second facilitator substance having a concentration effective for aiding in the infusion of the first substance into said at least one cell whose concentration is greater than 20% of the total composition. The specification teaches the claimed method for stabilization of cells in a vaginal swab samples (page 7, lines 7-9 and 24-26). Additionally, the specification teaches specific cell types found in vaginal fluid i.e. *Trichomonas vaginalis*, *Gardnerella vaginalis* and *Candida albican* and the specification teaches the claimed methods stabilize the structure and nucleic acids in these cell types (pages 11-12, Examples 2 & 4-12). The specification suggests the method "could be used for other biological specimens" (page 4, lines 26-29). However, the specification does not teach the method stabilizes the structure and nucleic acids of other specimens in the very large genus of cells as claimed. The claimed cells encompasses eukaryotic cells which further encompasses plant and animal cells each of which further encompass numerous species and sub-species, prokaryotic cells which further encompasses bacteria which further encompasses numerous species not described in the specification. The specification fails to teach a representative number of the claimed species. The specification teaches various formulations of the claimed method composition and experimental conditions

using the compositions (Examples 4-12) but the specification does not teach using the claimed method with a representative number of the claimed cell species.

Additionally, the claimed composition encompasses a very large genus of compositions not disclosed or described in the specification. The claims are drawn to a first substance whose concentration is less than 80% of the total composition; and a second facilitator substance whose concentration is greater than 20% of the total composition. The claimed concentrations encompasses a very large genus of compositions wherein the first substance has a concentration ranging from 0.001% to 79.99% encompassing all minor variations between 0.001% to 79.99% and the second substance has a concentration ranging from 20.001% to 99.99% encompassing all minor variations between 20.001% to 99.99%. The specification teaches 80% methanol/20% DMSO; 50% methanol/50% DMSO; and 100% methanol; 40% methanol + 40% ethanol/ 20% DMSO; 25% methanol + 25% ethanol/ 50% DMSO; and 80% ethanol/20%DMSO; 20% methanol/80% DMSO; 40% methanol/60% DMSO; 60% methanol/40% DMSO; 100% methanol; and 100%DMSO (Examples 4-12, pages 14-19, 21 & 23). However, the claimed compositions encompass an extremely large genus of compositions not disclosed in the specification.

Therefore, because the specification does not teach a representative number of the very large genus of claimed compositions and does not teach a representative number of the large genus of claimed cell species, the specification does not teach the specification does not provide a written description of the claimed composition in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The courts have stated that the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonable conclude the inventor had possession of the claimed invention see *In re Vas-Cath*, Inc. 935F2d. 1555, 1563, 19 USPQ2d 1111,1116. It is suggested that the claims be amended to claim the

invention as described in the specification e.g. by inserting "in vaginal fluid" after "one cell" in line 2 of Claim 13.

Response to Arguments

6. Applicant argues the above rejection is incorrect because the specification teaches cell types listed in Example 13. The argument is not found persuasive because the cells subjected to one of the many claimed compositions (i.e. 1:1 methanol : DMSO) in Example 13 (i.e. two cell-types found in vaginal fluid, Human keratinocyte cell line, *Spodoptera fugiperda* insect cell line; and human buccal cells) were only analyzed visually for cell lysis (page 24, lines 13-16). The cells were not analyzed for stabilized cell structure and nucleic acids as claimed.

Second paragraph of 35 U.S.C. 112: Indefinite

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 21 & 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21 & 23 are indefinite in depending from canceled claim 17. It is suggested the claims be amended to depend from a pending claim.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 13-16, 18, 21-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gee et al. (U.S. Patent No. 6,162,931, filed 12 April 1996), Williams et al. (Journal of Clinical Microbiology, 1995, 33(6): 1558-1561), Connelly et al. (U.S. Patent No. 5,422,277, filed 27 March 1992) Tometsko (U.S. Patent No. 5,229,265, filed 13 March 1990), Evinger-Hodges et al. (WO 90/02204, published 8 March 1990) and Bresser et al. (U.S. Patent No. 5,521,061, filed 17 July 1992).

Regarding Claim 13, Gee et al. teach a method for stabilizing the structure and nucleic acids of at least one cell in a sample (i.e. fix and permeabilize, Column 30, lines 54-56) comprising; adding to a vessel containing the sample a composition comprising a first substance having an effective concentration for precipitating or denaturing proteins comprising alcohol i.e. a fixative solution comprising methanol, and a second facilitator substance having an effective concentration for aiding in the infusion of said first substance into said cell i.e. DMSO (Column 30, lines 46-60); contacting said cell in said sample with said composition; incubating said sample with said composition for an effective period of time and at an effective temperature and obtaining said at least one cell with stabilized structure and nucleic acids (Column 74, lines 41-42) wherein the methanol stabilizes cell by fixation and the DMSO permeabilizes the cell to facilitate infusion in to the cell (Column 30, lines 49-60) but they do not teach the concentrations of the first and second substance wherein the combined concentrations is 100% of the composition. However, as noted by Gee et al. (Column 30, lines 46-51), the prior art is replete with methods and compositions for fixing cells so as to preserve cellular morphology by stabilizing cell structure and nucleic acids and to permeabilize so as to facilitate transport across the cell membranes wherein the concentrations of the components of the compositions vary greatly relative to cell type and desired results. For example, Williams et al. teach a method for stabilizing the structure and nucleic acids of a cell (i.e. bacterial cells) comprising a composition comprising at least one alcohol (i.e. ethanol) which is effective for precipitating or denaturing proteins wherein the concentration is less than 80% (i.e. 50, 70%,

75%) of the total composition (page 1558, right column, third full paragraph); Connelly et al. teach a method for stabilizing the structure and nucleic acids of a cell (i.e. prokaryotic and eukaryotic cells (Column 9, lines 20-22) comprising a composition comprising a facilitator substance i.e. DMSO whose concentration is greater than 20% i.e. about 20% (Column 7, line 61-Column 8, line 2); Tometsko teaches a method for stabilizing the structure and nucleic acids of a cell (red blood cells) comprising a composition comprising at least one alcohol i.e. methanol (Column 7, lines 5-29) wherein the method further comprises a second facilitator substance i.e. DMSO(Column 6, lines 66-68); Evinger-Hodges et al. teach a method for stabilizing the structure and nucleic acids of a cell comprising a composition comprising a fixative solution for optimal fixation (page 4, lines 22) comprising an alcohol and a facilitator substance i.e. 50% methanol/50% acetone (page 13, lines 24-35) wherein Gee et al. teach acetone is a facilitator effective for aiding infusion (Column 30, lines 54-56); and Bresser et al. teach a method for stabilizing the structure and nucleic acids of a cell comprising a composition comprising at least one alcohol and a second facilitator substance i.e. DMSO wherein the concentrations of the components are variable (Column 2, lines 19-33). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply teachings generally known within the art to modify the fixative solution of Gee et al. and by routine experimentation alter the composition components and component concentrations to thereby optimize experimental results. It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 14, Gee et al. teach the method wherein the alcohol is methanol (Column 30, lines 46-49).

Regarding Claim 15, Gee et al. teach the method wherein the second substance is dimethyl sulfoxide (DMSO) (Column 30, lines 54-56).

Regarding Claim 16, Gee et al. teach the method wherein the first substance is comprised of one alcohol (Column 30, lines 46-49).

Regarding Claim 18, Gee et al. teach the method wherein the first substance is comprised of one alcohol (Column 30, lines 46-49) but they do not teach the first substance is comprised of a first alcohol or ketone and a second alcohol or ketone. However, Tometsko teaches the similar method wherein the first substance comprises a first alcohol and a second ketone i.e. methanol/acetone (Column 7, lines 27-29). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the first substance comprising one alcohol as taught by Gee et al. to further comprise a second ketone as taught by Tometsko based on cell type being stabilized for the obvious benefit of optimizing stabilization for the specific cell-type.

Regarding Claim 19, Gee et al. do not teach the first substance is comprised of a first alcohol or ketone and a second alcohol or ketone. However, Tometsko teaches the similar method wherein the first substance comprises a first alcohol and a second ketone i.e. methanol/acetone (Column 7, lines 27-29) but they do not teach a ratio for the components of the composition. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the first substance comprising one alcohol as taught by Gee et al. to further comprise a second ketone as taught by Tometsko and using routine experimentation optimize the ratio of component in the composition for each specific cell type to be stabilized for the obvious benefit of optimizing stabilization for the specific cell-type and maximize experimental results.

Regarding Claim 20, Gee et al. teach the method wherein the first substance is comprised of one alcohol (Column 30, lines 46-49) but they do not teach the ratio or the components in the composition. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the ratio of the components in the composition taught by Gee et al. using routine experimentation optimize the ratio of

component in the composition for each specific cell type to be stabilized for the obvious benefit of optimizing stabilization for the specific cell-type and maximize experimental results.

Regarding Claim 21, Gee et al. teach the method wherein said first substance is methanol and said second substance is DMSO (Column 30, lines 46-56). For purposes of examination, Claim 21 is interpreted as depending from Claim 13.

Regarding Claim 22, Gee et al. teach the method wherein said first substance is methanol and said second substance is DMSO (Column 30, lines 46-56) but they do not teach the method wherein the first substance comprises a first alcohol and a second ketone i.e. methanol/acetone (Column 7, lines 27-29). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the first substance comprising one alcohol as taught by Gee et al. to further comprise a second ketone as taught by Tometsko based on cell type being stabilized for the obvious benefit of optimizing stabilization for the specific cell type.

Regarding Claim 23, Gee et al. teach the method wherein said first substance is methanol and said second substance is DMSO (Column 30, lines 46-56) but they do not teach the first substance is ethanol. For purposes of examination, Claim 21 is interpreted as depending from Claim 13. Williams et al. teach the similar method comprising ethanol (page 1558, right column, third full paragraph) and Bresser et al. teach that methanol and ethanol are similar precipitants (Column 7, lines 39-40). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the first substance comprising the precipitant, methanol as taught by Gee et al. by replacing the methanol with the precipitant, ethanol as taught by Williams et al. based their known similar properties of precipitation and based on available reagents for the obvious benefits of economy and based on cell-type for the obvious benefit of optimizing stabilization for the specific cell-type.

Regarding Claim 24, Gee et al. teach the method wherein said first substance is methanol and said second substance is DMSO (Column 30, lines 46-56). For purposes of examination, Claim 21 is interpreted as depending from Claim 13.

Regarding Claims 25-27, Gee et al. teach the method wherein RNA is stabilized (Example 127). Additionally, Evinger-Hodges et al. teach the method wherein DNA (Claim 25), RNA (Claim 26) and ribosomal RNA (Claim 27) is stabilized (page 6, lines 1-7). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made that to apply the methanol fixative method of Gee et al. to DNA, RNA and ribosomal RNA as taught by Evinger-Hodges et al. for the obvious benefit of stabilizing total cellular nucleic acids for the expected benefit of detecting multiple nucleic acids simultaneously as taught by Evinger-Hodges et al. (page 3, lines 29-31).

Regarding Claim 28, Gee et al. are silent with regard to effective period of time. However, Williams et al. teach the similar method wherein the effective period is about one day (page 1559, Fig. 1).

Regarding Claim 29, Gee et al. are silent with regard to effective temperature. However, Williams et al. teach the similar method wherein the effective temperature is room temperature (page 1560, left column, first full paragraph, lines 3-5).

Regarding Claim 30, Gee et al. are silent with regard to effective temperature. However, Williams et al. teach the similar method wherein the effective temperature from about 0°C to 40°C i.e. room temperature (page 1560, left column, first full paragraph, lines 3-5).

Regarding Claim 31, Gee et al. teach the method wherein said at least one cell is a prokaryote or eukaryote (Column 30, lines 17-20).

Regarding Claim 32, Gee et al. teach the method wherein said at least one cell is a microorganism i.e. bacterium or virus (Column 30, lines 17-20).

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
April 3, 2001

W. Gary Jones
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4/6/01